PATHOLOGIC BASIS of DISEASE

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stable angina, Prinzmetal's variant angina is characterized by ST-segment elevation during the vasospastic attack, reflecting transmural ischemia, and total to near-total reduction of blood flow through a major coronary artery. However, other attacks in the same patient may be characterized by ST-segment depression typical of stable AP.

Unstable angina, the third pattern, is the most ominous and has been called "preinfarction angina," "acute coronary insufficiency," and "accelerated angina." These patients are at great risk of suffering a myocardial infarction. Clinically, unstable AP is characterized by prolonged pain, the onset of pain at rest in an individual with stable angina, or significant worsening of the pain of stable exertional angina. Most often these manifestations are accompanied by ST-segment depression. On angiography there almost always is severe stenosing coronary atherosclerosis. The fact that some attacks of unstable angina occur at rest and are associated with ST-segment elevation, both characteristic of Prinzmetal's angina, makes evident the variable contribution of vasospasm to the causation of this form of angina.

By definition, in AP, whatever the clinical pattern, there are no large acute lesions of ischemic myocardial necrosis, but there may well be small foci of fibrous scarring, scattered subendocardial myocardial vacuolization, and sarcoplasmic resorption (myocytolysis) as evidence of significant ischemia or large scars of past episodes of myocardial infarction. Electrocardiographic and serum enzyme analyses (detailed on p. 564) further suggest that during an acute attack these patients often have *acute* myocardial injury that in large part is reversible. Biopsies obtained during cardiac surgery (coronary artery bypass grafting) reveal areas of reversible ultrastructural changes as well as, frequently, death by myocytolysis (p. 561) of scattered individual myofibers.[21] AP is thus of importance on two scores. It warns of serious myocardial ischemia and also makes clear that vasospasm is a potent contributor to coronary insufficiency.

MYOCARDIAL INFARCTION (MI)

Myocardial infarction is overwhelmingly the most important form of IHD and, indeed, cardiac disease in the United States and other industrialized nations. In 1979 about 60% of the deaths caused by IHD (p. 551) in the U.S. were attributable to MI. The remainder were caused by chronic ischemic heart disease, marked frequently by large myocardial scars from past episodes of MI. In the aggregate, then, MI accounts for 20 to 25% of all fatalities in atherosclerosis-prone societies. To place these deaths in some perspective, they exceed by many thousands those related to all forms of neoplasia collectively.

Mortality data do not tell the whole story. Each day in the U.S about 3400 individuals suffer a "heart attack" (myocardial infarct). In more personal terms, a North American male has a one in five chance of having an MI or dying suddenly from an acute ischemic eve before reaching the age of 65 years. It is painful evident that MI is the number one cause of death ar clinical challenge in affluent societies.

In the great majority of cases, widespread seve coronary atherosclerosis of the coronary arteries unde lies MI. In addition, some sudden event such as corc nary thrombosis must unfavorably alter the precariou balance (Fig. 13–3). Excessive exercise and increase myocardial demands can be documented in less tha 15% of instances. Alternatively, the myocardial supply can be suddenly reduced by a superimposed occlusive thrombosis or by vasospasm, but the precise frequency of these events is still uncertain. *Whatever the sequence of events, the imbalance between myocardial needs and supply induces an episode of acute myocardial ischemia having one of four possible consequences: (1) it may only induce an attack of angina; (2) more severe ischemia may result in myocardial necrosis limited to the inner one-third to one-half of some portion or the entire circumference of the left ventricular wall to produce multiple subendocardial foci of ischemic necrosis, also called a "subendocardial infarct"; (3) the ischemic necrosis may more or less traverse the entire thickness of some portion of the left ventricular wall, creating a "transmural infarct"; or (4) the acute ischemic event*

Figure 13–3. Cross section of a coronary artery narrowed by atherosclerosis. Rupture of a plaque at 2 o'clock has extruded atheromatous debris and initiated an occlusive thrombus within the lumen.

may cause "sudden cardiac death" within a few hours. Many of these sudden deaths are attributable to ischemia-provoked ventricular arrhythmias.

EPIDEMIOLOGY. Because of the dominating importance of coronary atherosclerosis in its pathogenesis, the epidemiology of MI is the epidemiology of atherosclerosis (p. 506). The striking geographic differences and the declining frequency in the United States and elsewhere in the mortality from ischemic heart disease, discussed earlier (p. 552), of necessity apply to MI, the principal cause of death from IHD. Whites are affected more often than blacks in the U.S., but for unknown reasons blacks tend to die of MI at an earlier age. *The incidence of fatal MI progressively rises with age* to peak in the 55- to 64-year-old group in males and in the eighth decade in females. Approximately 90% of all male deaths occur between the ages of 35 and 64. MI may occur in the very elderly, however, as well as in younger individuals, even in the third decade of life, particularly when such predispositions to atherosclerosis as hypertension, diabetes mellitus, familial hypercholesterolemia, and other causes of hyperlipoproteinemia are present. Virtually throughout life, males are at significantly greater risk than females, the differential progressively declining with advancing age. In the decade from 35 to 44 years, the death rate for white men is six times that for white women. In the next decade (45 to 54 years) there is a four- to fivefold difference, which falls to a twofold difference at ages 65 to 74.[22] *Except for those having some predisposing atherogenic condition, women are remarkably protected against MI during reproductive life.* However, there is now substantial evidence that the use of oral contraceptives, *as formulated in the past*, increases the risk of MI. The general data were presented on page 447. Up to the time of the studies, users who are 35 to 49 years of age have about a three- to fourfold greater risk than nonusers, and this increased risk does not appear to be related to duration of use.[23] For past users 40 to 49 years of age, the magnitude of the increased risk is related to duration of use. With less than five years of past use there is no persistent increased risk, but with long-term past use (five years or more) the risk is increased about twofold. In addition, oral contraceptives have been found to multiply the effects of other risk factors for MI such as cigarette smoking, which alone increases the risk 10- to 20-fold among young women.[24, 25] A recent report emphasizes that the risk of contraceptives may well have been exaggerated because of the difficulty in segregating their effects from other concurrent risk factors.[26] Cigarette smoking has a comparable effect among men.[27]

A number of other variables influence the risk and, therefore, the epidemiology of MI, but all must be categorized as somewhat controversial. Principal among these are personality structure, regular exercise, and alcohol consumption. A number of studies have claimed that so-called type A individuals—hard-driving, impatient, competitive, compulsive—are coronary prone. However, a recent panel concluded that the findings to date, although strongly suggestive, are not conclusive.[28] Equally uncertain is the value of exercise in the prevention of coronary heart disease and, in particular, MI.[29] Several reports contend that exercise conditioning, when regularly employed, reduces the rate of fatal heart attacks.[30] These epidemiologic studies have been buttressed by the demonstration that moderate conditioning exercise of monkeys on an atherogenic diet reduces the severity of coronary atherosclerosis. Whether the physical activity in humans acts in a similar fashion or instead increases the capacity of the coronary arterial supply or its anastomoses is still uncertain. It is relevant that the level of high-density lipoprotein (HDL) is increased with exercise, which, as discussed on page 514, is inversely correlated with atherogenesis. Physical conditioning may also augment the fibrinolytic response and thereby provide a potential protective mechanism against the development of thrombi within coronary arteries.[31] So it well may be that the joggers shall inherit the earth. Moderate alcohol consumption, which is also associated with increased HDL levels, has likewise been accorded a protective role. Attractive as this last notion may be to sedentary authors, the putative beneficial effect of moderate alcohol consumption is far from proven.

PATHOGENESIS. Consideration of the pathogenesis of MI involves analysis of the sequence of events leading to the critical imbalance between the myocardial perfusion and demands. It has already been pointed out (p. 552) that severe acute ischemic episodes may have one of four consequences: (1) angina pectoris, (2) a subendocardial infarct, (3) a transmural infarct, or (4) sudden death. The first of these has already been discussed (p. 555). The remaining three require separate consideration since they have somewhat different origins.

There is general agreement that subendocardial infarction is the consequence of global myocardial hypoperfusion secondary to severe stenosing atherosclerosis of at least two, and more often all three, major coronary trunks.[32] There is further agreement that an occlusive thrombus is present in less than 10 to 20% of cases (some say rarely).[14, 33] You may recall that the subendocardial region of the myocardium works harder and is less well perfused than the outer layers (p. 553). It is proposed, therefore, that with severe stenosing bi- or tri-vessel disease, a state of chronic marginal blood flow exists. Further reduction in flow, as might occur with episodes of congestive heart failure, hypotension, cardiac arrhythmia, or any increase in myocardial demand from exercise or disease-induced tachycardia, would then tip the balance to induce irreversible damage. The extent of the subendocardial necrosis about the ventricular circumference would depend on the severity of narrowing of each of the major coronary trunks. Thus, if one vessel were relatively free of disease, the subendocardial necrosis might not encircle the ventricle.

The *pathogenesis of transmural MI* is much more controversial. The basic question is the precise nature

of the trigger event leading to the critical ischemic imbalance. Two views are equally ardently proposed. *The classic view holds that the dominating cause of acute MI is thrombotic occlusion of a coronary artery. Progressive atherosclerosis presumably leads in time to rupture or ulceration of an atheroma or an intraplaque hemorrhage as the trigger events inducing the thrombosis. More recently, the possibility has been raised that thrombosis is not necessary for infarction.* Conceivably, vasospasm or other mechanisms (detailed later) might cause the infarct and possibly be followed by thrombosis, or the vasospasm might initiate thrombosis. There is, however, agreement that in at least 90% of cases there is severe multivessel stenosing atherosclerosis with at least one, usually several, narrowings greater than 75% of the lumen.[34] Moreover, there is general agreement that infrequently increased myocardial demand or hypotension in the presence of severely narrowed coronary arteries may induce an acute infarct even in the absence of thrombosis. But what transpires with most transmural infarcts?

In support of the classic view, *many studies document thrombosis in 80 to 95% of acute myocardial infarcts overlying a stenosing complicated atheromatous plaque.*[33, 35, 36] Moreover, the thrombus is located at a site and in the vessel appropriate for the area of ischemic necrosis, suggesting cause and effect. Further support comes from a coronary angiographic study of patients within four hours of the onset of an apparent MI.[37] A totally occluded coronary artery was found in 87%, and proved to be caused by a thrombus in the great majority. When angiography could not be performed until 12 to 24 hours after the onset of symptoms, a total occlusion was found in only 65% of patients. This decreased frequency could imply lysis or disruption of a preexisting thrombus or, alternatively, release of vasospasm at the site of a thrombus, relieving the total occlusion.[37] These observations in living patients buttress the contention that thrombosis is usually the critical event in the production of a transmural infarct.

Arguments, however, have been presented against the critical role of thrombosis in the pathogenesis of MI. Many studies report finding thrombi in less than 55% (some would say only about 35%) of acute infarcts.[38, 39] If thrombosis is not requisite for the initiation of an acute transmural infarct, what is the trigger event inducing the necrosis? Only some plausible scenarios can be suggested. Vasospasm might be a mechanism, as pointed out in the discussion of angina pectoris (p. 555).[40–42] MI has been observed in relatively young males with no angiographically demonstrable coronary artery disease—not even stenoses.[43, 44] Infarcts have developed during or immediately following coronary angiography in locations appropriate for the segmental vasospasm observed during the angiography.[45] Moreover, thrombosis is sometimes found later at postmortem examination at the site of the spasm. Surprisingly, even atherosclerotic vessels may further narrow under the influence of vasospasm. There is, in addition, evidence that platelet activation and the release of vasoconstrictor substances such as thromboxane A_2 possibly serotonin may contribute to the vasospas Platelet activation might also result in microthro which, in the aggregate, could significantly reduce onary flow.[47] *The following sequence of events can be proposed. An episode of vasospasm known to transient and unpredictable from the study of m patients with Prinzmetal's angina causes a critical duction in coronary flow or damages a large athero exposing collagen and activating platelets. Platelet gregation may reduce myocardial perfusion, or release of vasoconstrictors (e.g., thromboxane A_2) fr the activated platelets might worsen vasospasm. By of these pathways an infarct results and, with or with a superimposed arrhythmia, reduces coronary per sion, potentiating the formation of a thrombus, logic at the site of vasospasm or possibly at a critical steno*

As pointed out earlier, sudden cardiac death (SC may follow any form of IHD, but study of these patie sheds some light on the possible pathogenesis of ac MI. The deaths are attributable to the sudden onset some fatal arrhythmia, usually ventricular fibrillati Presumably some acute ischemic event precipitated t arrhythmia in a heart already having precarious elect cal instability. A study of 923 individuals who we unconscious and pulseless when medical assistance rived revealed that most of the victims were in ventr ular fibrillation or asystole.[48] Fewer than 50% of t patients (some say as few as 13 to 28%) who a resuscitated after virtual SCD later have detectab acute MI.[49] But even when an infarct is later found, t question arises, did it initiate the arrhythmia, or was precipitated by it? The frequency of *acute* thrombi individuals who were temporarily rescued is related duration of survival following the onset of symptom and ranges from 10% to about 50% of cases.[50] Despi the usual absence of a major thrombotic occlusion, the frequently are platelet aggregates and microthrombi i the intramural coronary branches.[51] Moreover, *in ove 90% of cases there is extensive coronary atherosclerosi in at least one, and sometimes all three, coronary trunk more severe on the average than in controls.* In addition about one-half of the patients have evidence of an ol MI. It therefore is now believed that *most SCDs occu in individuals having severe coronary atherosclerosis often an old MI but only infrequently an acute MI Significantly, most have no acute major coronary occlu sion, but instead platelet-fibrin microthrombi. Thus, i appears that SCD, related to an arrhythmia, is caused by some acute ischemic event* that is not necessarily initiated by a thrombotic occlusion of a major coronary vessel.[52] It is possible, therefore, that a similar process, more severe or more prolonged, might lead to an acute MI.

We can go no further in unraveling the precise sequence of events. *Although in all likelihood coronary thrombosis is the major cause, it seems best to consider an acute transmural MI a multifactorial disorder related to influences acting singly or in combination that increase myocardial demand or decrease coronary per-*

mural infarct, and may then pursue the same evolving sequence of macroscopic and microscopic changes described for the transmural lesion.

Following the description of the transmural infarct and the subendocardial infarct, it is necessary to point out that, on occasion, both patterns are found in a heart. Typically, subendocardial infarction is present, involving a fairly large segment of the circumference with transmural extension in a more localized area. There is no way of ascertaining whether the transmural involvement followed on the heels of the subendocardial infarction, since both lesions often appear to be at the same stage of evolution. However, the possibility of a temporal sequence separated by a brief interval of time cannot be excluded. In some dogs, ligation of a coronary artery for 40 minutes produces subendocardial necrosis at first, but with increasing duration of coronary occlusion, the infarct tends to become transmural—referred to as the **"wavefront phenomenon."**[69] It is possible, therefore, that transmural infarcts begin with subendocardial necrosis that extends in some instances, depending on the severity and duration of the ischemia.

CLINICAL COURSE. The clinical diagnosis of acute MI is mainly based on three sets of data: (1) symptoms, (2) electrocardiographic (ECG) changes, and (3) elevations of specific serum enzymes, although other diagnostic modalities are available, e.g., radioisotope scanning. Typically, the onset is sudden and devastating with severe, constricting, crushing, burning, substernal or precordial pain that often radiates to the left shoulder, arm, or jaw. It is often accompanied by sweating, nausea, vomiting, or breathlessness. Occasionally, the clinical manifestations are much less specific and consist of burning substernal or epigastric discomfort that is interpreted as "indigestion" or "heartburn." In about one-third of patients the onset is entirely asymptomatic and the disease is only discovered later by routine ECG changes.

The ECG changes usually become evident from the outset of the attack, although they may be nondiagnostic in 20 to 25% of patients, depending on the location of the infarct, its size, and the number of ECG leads examined. The precise changes that may be encountered are too complex to be discussed here in detail, but basically they consist of new Q waves associated with evolving ST-segment and T-wave changes in transmural infarction, or only ST-segment and T-wave changes in the subendocardial infarct. As the infarct evolves, the ST segment normalizes and the T waves invert. A variety of arrhythmias also may be present, as will soon be pointed out. These may be present from the outset or appear in the course of the next few hours.

Alterations of serum enzymes are more sensitive and reliable indicators of myocardial infarction than ECG changes. Serum glutamic-oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), and creatine kinase (CK) levels are generally elevated following an infarct. All are soluble cytoplasmic enzymes that leak out of damaged myocardial cells. However, the diagnostic specificity of these enzymes is compromised because increased levels may be observed with noncardiac lesions, e.g., elevations of SGOT with pulmonary infarction and of LDH with hepatic necrosis. Much greater specificity can be achieved with the use of particular isoenzymes. There are five isoenzymes of LDH, identified as 1 through 5. In the normal individual the serum levels of LDH_1 are lower than those of LDH_2. A reversal of this ratio is usually apparent about 12 hours after the onset of an MI, and peaks in 48 to 72 hours. This reversal has been found to be about 90% sensitive and 95% specific for acute MI, and moreover it may persist for up to six days and can thus be useful in instances of recent post infarction. However, false-positive results may be encountered from in vivo and in vitro hemolysis or renal cortical necrosis. The most specific indicator of myocardial necrosis is elevation of the MB isoenzyme of CK.[70] This isoenzyme is found in significant concentrations only in heart muscle; normally, it cannot be detected in the serum or is present in minute amounts. Thus, significant elevations are variously reported in 85 to 95% of patients following an acute MI when samples are taken at the appropriate time. The mean appearance time of this isoenzyme is about seven hours post infarction (peak levels occur at about 19 hours) and it is eliminated in about 48 hours. The level of the elevation has been used as a parameter of the size of the infarct. With all enzyme determinations, the analytic techniques and time of sampling are critical.

Radioisotope scanning techniques have added another approach to the diagnosis of myocardial infarction. Although only used in special instances, they provide a method of mapping the infarct and therefore estimating its size. Most widely used are technetium^{99m}, pyrophosphate, and thallium-201. Technetium-labeled pyrophosphate apparently binds to the calcium phosphate in the matrix densities accumulating in the mitochondria of irreversibly damaged myocardial cells. Thallium, on the other hand, distributes in the heart in proportion to the myocardial perfusion. Thus, highest concentrations appear in normal myocardium while the infarct remains "cold." Both of these scintigraphic techniques yield false-positive and false-negative results and are considerably less widely used than isoenzyme determinations. Nonetheless, a totally normal scan is strong evidence against the diagnosis of acute MI.

After the onset of an acute ischemic event, one of several pathways may be followed. Regrettably, one is very brief and marked by SCD (25% of patients).[71] Indeed, SCD accounts for about 70% of all deaths caused by IHD. However, mobile coronary care units and effective resuscitation teams now "rescue" many of these victims. If the patient develops an acute MI and reaches the hospital, the spectrum can be presented as follows:*

1. Uncomplicated cases (10 to 20%).
2. Complicated cases (80 to 90%).
   A. Cardiac arrhythmias including conduction defects (90%).

*Modified from Yu, P. N.: The acute phase of myocardial infarction. Cardiovasc. Clin. 7:45, 1975.

B. Left ventricular congestive failure with mild-to-severe pulmonary edema (60%).
C. Cardiogenic shock (10 to 15%).
D. Rupture of free wall, septum, papillary muscle (1 to 5%).
E. Thromboembolism (15 to 20%).

Cardiac arrhythmias may appear at once and undoubtedly are responsible for many sudden deaths. Often they take the form of heart block, sinus bradycardia, sinus tachycardia, ventricular tachycardia, or ventricular premature contractions. Ventricular fibrillation is the most lethal, but prompt intervention by mobile and hospital coronary care units has succeeded in controlling this form of arrhythmia in about one patient in four or five.

The next most important clinical problem in terms of both survival and frequency is left ventricular dysfunction, which varies from little or no contractile incompetence to severe "pump failure"—cardiogenic shock. Most often there is some degree of left ventricular failure with hypotension, pulmonary vascular congestion and transudation into the interstitial pulmonary spaces. This mild failure may be transient, but in others it progresses to a serious threat when intra-alveolar pulmonary edema causes marked respiratory embarrassment and even cyanosis. The most severe extreme degree of "pump failure" usually becomes manifest when more than 40% of the left ventricle is infarcted. This is marked by a profound drop in cardiac output and blood pressure and the development of cardiogenic shock. Despite all heroic efforts to improve and sustain the circulation in these patients, the mortality rate is near 80%.

Were these hazards not enough, patients still confront the risk of myocardial rupture and mural thrombosis with peripheral embolization (Fig. 13–11). As pointed out, rupture may occur through the left ventricular free wall to produce massive hemopericardium, cardiac tamponade, and sudden death. Rupture through the interventricular septum may yield grave pulmonary consequences. Rupture of the papillary muscle and valvular dysfunction is another mechanism for severe congestive failure or cardiogenic shock. The prevention of peripheral embolism by anticoagulation is usually instituted but incurs the risk of bleeding (hemopericardium, hematemesis, hematuria).

It is difficult to express a prognosis for acute MI because of many modifying influences, e.g., age of patient, previous cardiovascular status, size and site of infarct, and manner of treatment.[72, 73] Only some generalities can be offered. As pointed out, some patients rescued from SCD are later found to have had an acute MI. Thus, some of the mortality related to acute infarction is "buried" within the category of SCD. Of those who are spared this catastrophe, about 10 to 15% succumb, usually in a hospital during the first four weeks. An additional 10% die during the first year, mostly of recurrent MI or cardiac failure. There is a continued three- to fourfold excess mortality in subsequent years, related to recurrent MI and cardiac failure.

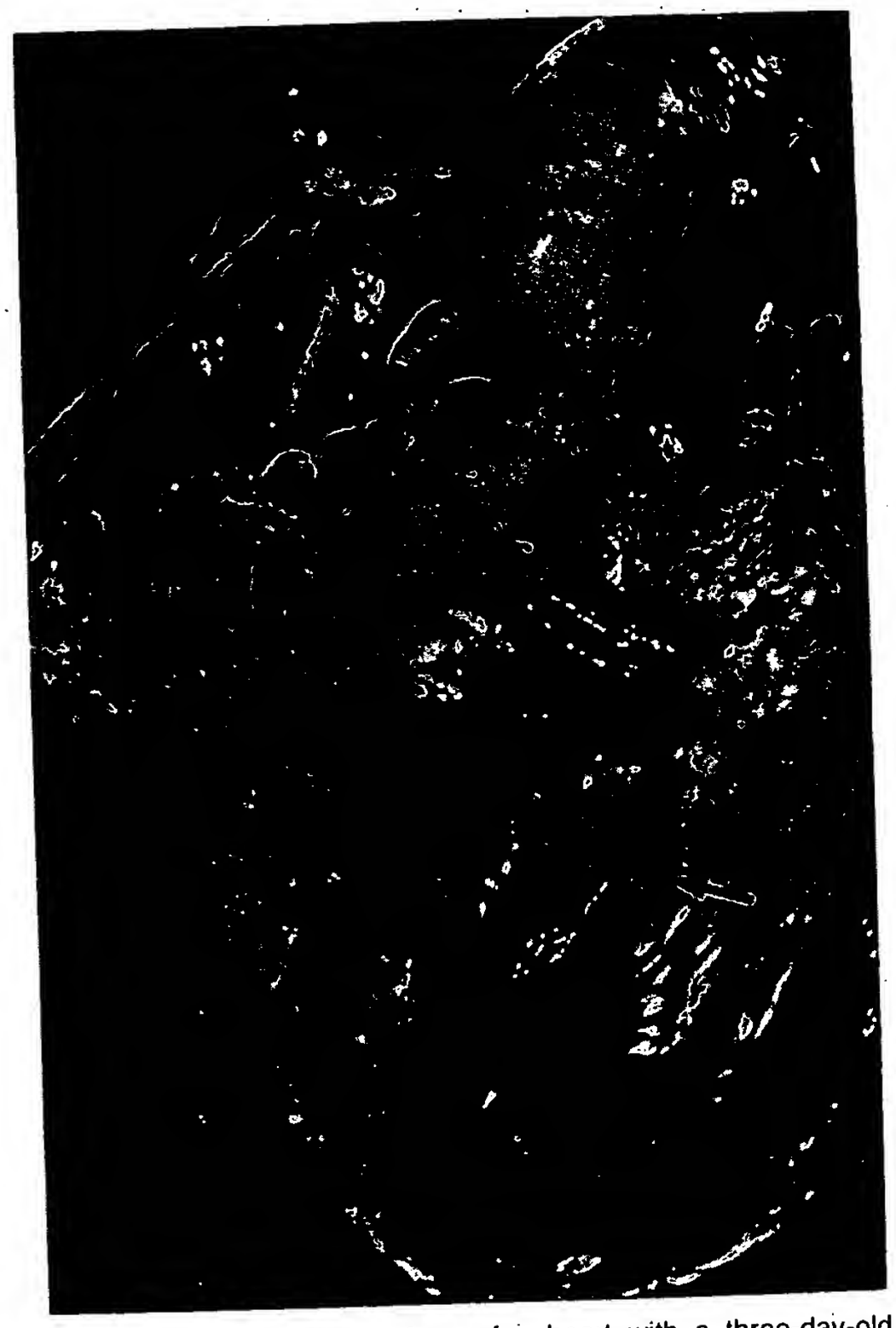

Figure 13–11. External surface of a heart with a three-day-old infarct. Dark linear tear *(arrow)* communicates with a rupture of anterior free wall of left ventricle.

Many efforts have been made to lower the incidence of MI in patients known to already have advanced coronary artery disease by reducing the major risk factors for coronary atherosclerosis (hypertension, hypercholesterolemia, and cigarette smoking). The results to date of these "secondary prevention" programs have been disappointingly equivocal. However, a very recent "primary prevention" study has been completed of men not having had any previous acute coronary events.[73A] It was focused only on lowering the hypercholesterolemia when it was above the level of 265 mg per dl of blood. Modest restriction in dietary cholesterol intake was instituted combined with cholesterol-lowering drugs (e.g., cholestyramine) and the incidence of nonfatal and fatal MIs was reduced by 20% compared with a carefully matched control group. This result is the first striking demonstration that the attack rate of MI can be lowered.

A substantial effort is also being made to improve the outlook by reducing or limiting the size of MIs with acute interventions. A variety of approaches have been used: (1) direct infusion of fibrinolytic agents, e.g., streptokinase, into the coronary arteries during the early hours after infarction to lyse thrombi;[74] and (2) agents

to beneficially effect coronary perfusion, myofiber integrity, or myocardial metabolism, e.g., hyaluronidase, beta blockers, glucose-insulin-potassium, or corticosteroids.[75, 76] A major difficulty has been proof of reduction in infarct size in the living patient. Nonetheless, improvement in immediate postinfarction survival has been demonstrated.

The long-term prognosis has also been materially improved by regimens to reduce the frequency of SCD and recurrent MI in patients during the year or two following acute infarction.[77] The many approaches in current use can be only briefly mentioned—beta-adrenergic blockage (e.g., propranolol, timolol); calcium-channel blockers that, in addition to their negative inotropic and chronotropic effects, induce vasodilation (e.g., nifedipine, verapamil); anticoagulant therapy; and antiplatelet aggregating agents (aspirin, sulfinpyrazone). Significant reductions (on the order of 25 to 50%) have been achieved in the mortality from SCD and recurrent MI.[78] Still controversial is the bypass of coronary occlusions with venous grafts in an attempt to improve perfusion and prevent primary or recurrent infarction.[79] Coronary artery bypass grafts are subject to progressive intimal fibrosis, occasional thrombosis, and even atherosclerosis, but at least 60 to 80% remain patent for five or more years. It is clear that patients with ischemic heart disease are victims of an all-too-common and all-too-fatal disease, but at the same time the beneficiaries of intensive efforts to improve their outlook.

CHRONIC ISCHEMIC HEART DISEASE (CIHD)

Slow, progressive atherosclerotic encroachment on the blood supply to the myocardium may induce the insidious onset of CHF in the elderly. Frequently, one or more MIs have punctuated this course. This pattern of IHD is characterized anatomically by diffuse myocardial atrophy, loss of myocardial cells (singly and in clusters), diffuse myocardial fibrosis, and sometimes one or more large areas of scarring from past episodes of infarction. In the past, this entity has been known by a variety of terms—"aging" heart disease, atherosclerotic heart disease, and ischemic cardiomyopathy—but all are unsatisfactory. It is not the inevitable consequence of advancing years. The term "atherosclerotic heart disease" logically would also include acute infarction and AP. Cardiomyopathies, by definition, exclude myocardial damage related to coronary atherosclerosis, so the term CIHD is currently favored.

Chronic ischemic heart disease is a major cause of cardiac failure and death. It is responsible for about 40% of the mortality related to IHD, and in 1979 caused almost 250,000 deaths in the United States. In the absence of attacks of AP or acute infarction, this condition may remain entirely unsuspected until slow, progressive cardiac decompensation appears. There is an unfortunate tendency to ascribe cardiac failure to CIHD when other causes for heart failure cannot be identified. It is a distinctive form of cardiac involvement, having well-defined morphologic changes.

The heart in this condition may be normal, smaller than normal in size, or even hypertrophied. The pericardial surface is unaffected, but there may be some atrophy of subepicardial fat commensurate with the loss of subcutaneous adipose tissues encountered in very aged individuals. Almost invariably, there is moderate-to-severe stenosing atherosclerosis of the coronary arteries. There may even be foci of total occlusion, possibly resulting from organized thrombi. The myocardium is often browner than usual or may be of normal color. Scars may be grossly visible, but typically they are not more than 0.5 to 1.0 cm in diameter, almost always confined to the left ventricle. Occasionally there is an obvious well-healed infarct. The left ventricle is usually dilated. The left ventricular wall will vary in thickness, depending on the duration of failure and the extent of the myocardial adaptive changes. The mural endocardium is generally unremarkable, but there is often slight fibrous thickening of the valves of the left side of the heart sufficient to make the leaflets lose their normal translucence. The chordae tendineae of the mitral valve may be comparably thickened but are not fused or significantly shortened, as is characteristic of healed rheumatic heart disease. Heavy calcification of the mitral annulus behind the valve leaflets and piled-up masses of calcium within the sinuses of the aortic leaflets may both be present, but these valvular changes are accompaniments of the aging process and are not clearly related to ischemic injury.

The major microscopic findings are myocardial atrophy, myocytolysis of single cells or clusters of cells, and diffuse small scars, particularly about vessels (Fig. 13–12).[80] The overall decrease in size of the myocardial cells is difficult to appreciate but is made most apparent by a subtle, intercellular fibrosis and the increase in yellow-brown perinuclear lipofuscin—"aging"—pigment. Some myofibers may be en-

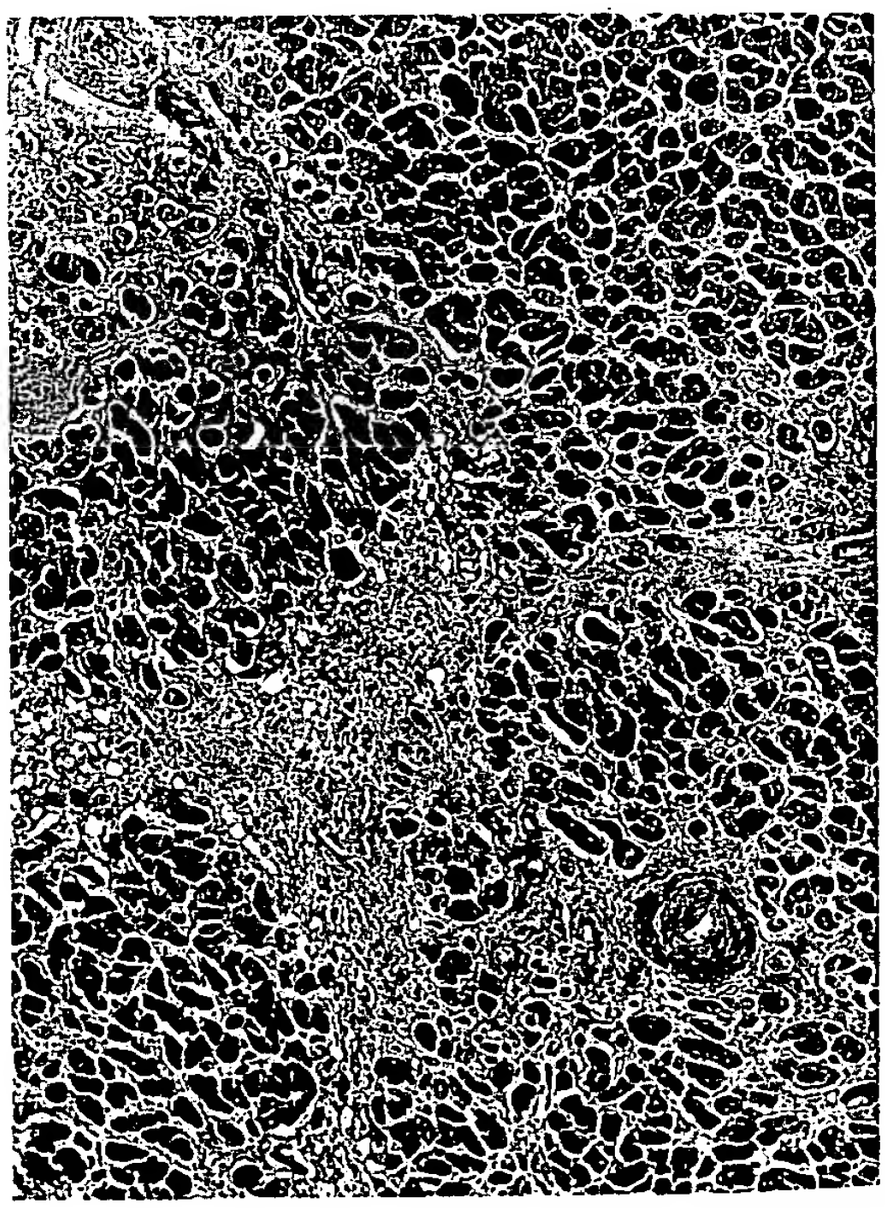

Figure 13–12. Patchy fibrous scarring principally about blood vessels of myocardium in CIHD.

larged owing to compensatory hypertrophy. Myocytolysis with resorption of sarcoplasm creates clear cytoplasmic large vacuoles or empty sarcolemmal sheaths. Collapse of the empty sheaths contributes to the appearance of the diffuse fibrosis. Large, healed myocardial scars may be present as the result of earlier episodes of acute infarction. **It is the concurrence of atherosclerotic narrowing of the coronary arteries, spotty myocytolysis, diffuse and small myocardial scars, and the changes of cell atrophy that delineates the diagnosis of CIHD.**[32]

Clinical Course. This form of heart disease is completely asymptomatic until its presence becomes manifest by the insidious appearance of cardiac decompensation, as the cardiac reserve is depleted fiber by fiber. Often it is discovered only as an incidental finding at autopsy. Some patients, however, have had attacks of angina or remote episodes of MIs. Occasionally the onset of congestive failure is more sudden and follows a precipitating illness such as pneumonia or some other form of debilitating disease. Failure, when it becomes manifest, is initially left-sided but ultimately leads to right-sided cardiac decompensation as well.

The clinical diagnosis of CIHD is made largely by the insidious onset of failure in patients who have had past episodes of MI or anginal attacks. In the absence of such evidence of severe coronary atherosclerosis, the diagnosis must rest on the exclusion of other forms of cardiac involvement in patients of advanced age.

The electrocardiographic changes merely confirm diffuse myocardial disease, sometimes with conduction bundle-branch blocks. Such murmurs as may be present are more likely related to left-sided ventricular dilatation with subsequent valvular regurgitation or to concurrent but unrelated calcific valvular changes. Generally, the congestive failure progresses slowly over the course of many years. However, a serious cardiac arrhythmia or an infarction may supervene and cause death. Patients with this condition may die of entirely unrelated causes before the cardiac involvement becomes symptomatic. It must be appreciated that in this geriatric group, patients rarely have one disease, and most often the manifestations of CIHD are intermixed with those related to all the other problems of these "not-so-golden years."

HYPERTENSIVE HEART DISEASE (HHD)

The minimal criteria for the diagnosis of HHD are (1) left ventricular hypertrophy in the absence of other cardiovascular pathology that might reasonably induce it and (2) a history of hypertension. Straightforward as this may sound, there are complexities. Hypertension strongly predisposes to atherosclerosis, and so most patients with elevated blood pressure have significant coronary atherosclerosis. It is difficult then, if not impossible, to segregate the contributions of ischemic injury with compensatory hypertrophy from those of hypertension in the induction of the cardiac enlargement. Equally bothersome is the concurrence of hypertension and some other form of heart disease in an individual with cardiac enlargement. By definition, *the diagnosis of HHD cannot be made when there is some other cause for hypertrophy,* such as aortic valvular stenosis, yet the hypertension may have contributed significantly to the hypertrophy and cardiac failure. Another problem, the definition of hypertension, is better left to clinicians and statisticians. Suffice it to note that the World Health Organization has designated 160/95 mm Hg as the dividing line, but these levels may be too high. In the Framingham Study, subjects having blood pressure readings between 140/90 and 160/95 had twice as much cardiovascular disease over the subsequent 18 years as the control group.[81]

Complexities notwithstanding, HHD is today the second most common cause of cardiac death, albeit totally overshadowed by IHD. In the United States in 1978 it caused about 7000 deaths. However, it should be noted that hypertension-accelerated coronary atherosclerosis contributes significantly to many of these deaths. About 30 to 50% of untreated hypertensives die of heart disease, and the remainder of stroke, hypertensive renovascular disease, and vascular complications (e.g., atherosclerotic aneurysms), in descending order. The mortality from hypertension and HHD over the past decades has declined in the U.S., and more among whites than among blacks. Much of this decline can reasonably be attributed to improved case finding and treatment of hypertension, but it is of interest that the decline began before effective methods of antihypertensive therapy came into wide use. Nonetheless, hypertension remains a major health problem. In the mid-1970s it was estimated that about 50% of blacks and 35% of whites in the U.S. over the age of 55 had a systolic blood pressure of at least 160 or diastolic pressure of at least 95.

Pathogenesis. The etiology and pathogenesis of hypertension are considered on page 1041. Here we are concerned with its effect on the heart. The blood pressure level is governed by the cardiac volume output and outflow resistance. The major components of the latter are peripheral arteriolar resistance, compliance of the large arteries, and the viscosity and inertia of the blood, all of which create resistance to the systolic ejection of blood from the left ventricle. High blood pressure places a so-called pressure overload on the left ventricle (much like aortic stenosis; aortic regurgitation, by contrast, imposes a volume overload). It does so largely by increasing the resistance to left ventricular outflow, mostly by widespread arteriolar vasoconstriction;[82] hence, the effectiveness of vasodilators in the reduction of elevated blood pressure. Once initiated, the increased blood pressure tends to rise progressively. Hypertension accelerates the development of atherosclerosis, reducing large vessel compliance, and induces thickening of the walls of small arteries and arterioles (see arteriolosclerosis, p. 518). The vascular disease in turn increases peripheral resistance and viscosity-related frictional drag. The heart, then, must maintain a normal cardiac output against this increased peripheral resis-